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ABSTRACT

An investigation was made of the behavioral effects of caffeine in a sample of 313 newborns and their mothers. A weighted measure of caffeine based on daily ingestion of coffee, tea, and cola was derived from a maternal interview. The majority of mothers consumed the equivalent of about 1.3 cups of coffee per day. Infant outcome measures included birth size, gestational age, and behavior as measured by the Brazelton Neonatal Behavioral Assessment Scale. To control for potential confounding variables possibly responsible for any observed caffeine effects, a list of 30 potential confounds was compiled. All control variables that correlated with a given substance at an alpha level less than or equal to .10 were considered potential confounds and included in regression analyses. Results showed that maternal caffeine consumption prior to pregnancy predicted lower birthweight, poorer orientation, and greater arousal and irritability. Each of these outcomes, except orientation, was related to exposure in a dose-dependent fashion. Related research found that infants whose mothers consumed higher levels of caffeine while breastfeeding had higher motor development scores than infants of mothers consuming lower levels of caffeine. Additionally, a study of the reliability and validity of maternal report of caffeine use indicated that, while women had the most difficulty recalling their consumption of caffeinated soft drinks during pregnancy, their reports were quite reliable regarding coffee and tea. (RH)

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EFFECTS OF PRE- AND POSTNATAL CAFFEINE EXPOSURE ON HUMAN INFANTS

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Neonatal Correlates of Intrauterine
to Smoking, Caffeine, and Alcohol

Caffeine crosses the placenta and has been detected in the plasma and urine of human newborns (Morris & Weinstein, 1981). It is recognized as an animal teratogen related to increased fetal mortality, decreases in fetal weight, and skeletal malformation in offspring of rats and mice treated during pregnancy (Food and Drug Administration, 1980; Palm et al., 1978; Thayer & Palm, 1975). Behavioral effects involving increased exploratory activity and poorer initial performance on operant conditioning tasks have also been found in rats long after caffeine exposure in utero and during lactation was terminated (Sobotka, Spaid, & Brodie, 1979). However, the implications for human newborns are unclear due to differences in mode of exposure, amounts consumed, and the metabolism of different species. Notwithstanding, the U. S. Food and Drug Administration (1979) has advised limiting caffeine consumption during pregnancy. Is this warning warranted?

To date, there has been little research on the effects of intrauterine exposure to caffeine on human newborns. One recent study (Linn, Schoenbaum, Monson, Rosner, Stubblefield, & Ryan, 1982) found no relation between coffee and tea consumption during the first trimester and malformations in the neonate, but another found heavy coffee consumption (8 cups or more per day) to be associated with birth defects (Borlée, Lechat, Bouckaert, & Misson, 1978). Lower birth weight has also been related to caffeine consumption during pregnancy (Hogue, 1981).

The only behavioral data available on human newborns come from Streissguth's laboratory and our own. Streissguth and her associates found a

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negative relationship between maternal caffeine use during pregnancy and an activity/motor maturity factor on the Brazelton neonatal scale, administered at 1-2 days after birth (Streissguth, Martin, & Barr, 1978). Offspring of heavy caffeine users were characterizied by lower activity levels and poorer muscle tone and motoric development.

Our study investigated the behavioral effects of caffeine in a sample of women who consumed little or no alcohol. Various issues were addressed. For example, one consideration in assessing the teratogenic potential of a substance is whether ingestion prior to pregnancy merits the same attention as exposure during pregnancy. Most investigators assume that any abnormal deficits will be attributable to ingestion during pregnancy, and abstinence during pregnancy does reduce the effect of smoking on birth size and behavior (Landesman-Dwyer & Emanuel, 1979; Lowe, 1959; U. S. Public Health Service, 1979). However, a history of alcohol abuse has been shown to affect neonatal outcomes even when the mother abstains during pregnancy or consumption during pregnancy is statistically controlled (Little, Streissguth, Barr, & Herman, 1980; Jacobson, Fein, Jacobson, Schwartz, & Dowler, 1984). We were also interested in knowing whether effects associated with caffeine use persist after demographic and other confounding variables are statistically controlled. Are behavioral effects directly related to caffeine use or by-products of the infant's physical condition, such as reduced birth size, and are the effects related to caffeine use in a dose-dependent fashion?

Our study included 313 newborns and their mothers, recruited on the first or second day following delivery as part of a longitudinal study on prenatal exposure to an environmental toxin, polychlorinated biphenyls (PCBs) (see Fein, Jacobson, Jacobson, Schwartz, & Dowler, 1984; Jacobson, Jacobson, Fein, Schwartz, & Dowler, 1984).

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A weighted measure of caffeine based on daily ingestion of coffee, tea, and cola was derived from a maternal interview (see Table 1.) Because of its higher caffeine content coffee was given a weight three times that of tea and cola. We have found that this weighted measure is superior to an unweighted measure in predicting infant outcome and is as effective as a more detailed measure that takes into consideration type of coffee preparation, size of cup, etc. (see Dowler & Jacobson, 1984). Infant outcome measures included birth size, gestational age, and behavior based on the Brazelton Neonatal Behavioral Assessment Scale (1973), administered on the third day following delivery (Table 2). The sample was Caucasian and predominantly middle class and married.

While 69% of the women abstained from smoking during pregnancy and 81% consumed no alcohol, as can be seen in Figure 1, the majority (84%) consumed caffeine, averaging 113 mg, the equivalent of about 1.3 cups of coffee per day (SD = 123 mg, range = 0-520 mg). Ninety percent consumed caffeine prior to pregnancy, averaging 182 mg or 2.2 cups of coffee per day (SD = 185 mg, range = 0-800 mg).

In order to control for potential confounding variables which might be responsible for any observed caffeine effects, a list of 30 potential confounds was compiled from maternal interview and hospital records. All control variables which correlated with a given substance at an alpha level less than or equal to .10 were considered potential confounds and included in our regression analyses (see Table 3).

As shown in Table 4, maternal caffeine consumption prior to pregnancy predicted lower birthweight, poorer orientation, and greater arousal and irritability, even after the effects of caffeine use during pregnancy and the

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potentially confounding variables were controlled. Each of these outcomes, except orientation, were related to exposure in a dose-dependent fashion (see Figure 2). Arousal and irritability were clearly not a consequence of the smaller birthsize of the more highly exposed infants.

Thus, the results of our study and those of Streissguth suggest that subtle behavioral effects associated with caffeine use may be evident in the newborn even in the absence of physical or gestational age effects. While the effects of some drugs, like smoking,on the fetus seem relatively direct, the effects of caffeine may be mediated by alterations in maternal function that occur prior to conception. Alternatively, the present effects may be due to damage that occurs after conception but before the mother recognizes she is pregnant.

Whether these neonatal behavioral outcomes predict longterm developmental deficits is not yet clear. Moreover, caffeine exposure continues postnatally among nursing infants, and the young infant metabolizes caffeine much more slowly than the adult (Soyka, Neese, Main & Main, 1981). Little research exists on the effects of caffeine exposure via breast-feeding, although there have been some reports of increased irritability and sleeping problems (Berkowitz et al., 1981; Hill et al., 1977). Similarly, preterms treated for apnea with theophylline, which is metabolized to caffeine, have been described as more wakeful, more alert, and experiencing less active sleep even one month after the theophylline treatment ended (see Thoman et al., 1984). However, there is evidence suggesting that such effects will be potent only in particularly immature organisms. Also, longterm effects on standardized developmental tests were not found to be associated with theophylline exposure.

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In order to see whether any of the neonatal deficits persisted, as part of his doctoral dissertation, Jeffrey Dowler looked at the effects of prenatal caffeine exposure and exposure to caffeine via breastfeeding in 179 infants seen in our follow-up study at 5 months. The mothers of these infants completed a detailed mail-in questionnaire regarding postnatal caffeine exposure and breastfeeding patterns. Bayley mental development and psychomotor development scores were not affected by the mother's prenatal caffeine consumption. Nor were the mental scores affected by exposure to caffeine through breastfeeding. However, infants whose mothers consumed higher levels of caffeine while breastfeeding had higher motor development scores F (3,163) = 2.98, p <.05, even after 5-month length and weight and potential confounds were controlled.

To summarize, these data suggest some subtle behavioral effects related to heavy caffeine use, that is, when the mother consumes the equivalent of at least 4-6 cups of coffee daily. These results, therefore, indicate a need for further research on the effects of heavy consumption. However, due to recent adverse publicity regarding caffeine effects on newborns, such women are becoming difficult to locate. In a small study examining the reliability and validity of maternal report of caffeine use, we interviewed 57 Caucasian women in an urban Detroit Hospital. The majority expressed concern about the possible dangers of caffeine use, and these women had decreased their consumption levels during pregnancy to lower levels than in our previous sample surveyed only three years earlier. Such concern was expressed by informed wives of physicians, as well as uneducated, lower class women.

In research of this kind, a major issue concerns how reliable and valid is the mother's report. Test-retest reliability for maternal report of caffeine

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use before and during pregnancy obtained shortly after delivery and 6 weeks later was .78 and .33 for the caffeine summary measures, respectively. As can be seen in Table 5, women had most difficulty recalling caffeinated soft drinks during pregnancy, but were quite reliable regarding coffee and tea.

Validity of maternal report was assessed by asking mothers to keep a diary of their caffeine intake for 7 days and comparing these data with the maternal report of caffeine use obtained earlier. The results suggest that the questionnaire is a valid measure for coffee and tea but less so for caffeinated soft drinks (Table 6).

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TABLE 1

MEASURE OF CAFFEINE CONSUMPTION

THE MOTHERS WERE ASKED HOW MUCH COFFEE, TEA, AND COLA THEY CONSUMED BEFORE AND DURING PREGNANCY. THE FOLLOWING EQUATION WAS USED TO ESTIMATE BOTH CAFFEINE MEASURES:

$$[(1 \times \text{CUPS OF COFFEE PER DAY}) + (1/3 \times \text{CUPS OF TEA PER DAY}) + (1/3 \times \text{SERVINGS OF COLA PER DAY})] \times 84 \text{ MG} = \text{MG CAFFEINE CONSUMED PER DAY}$$

THE ESTIMATE IS BASED ON DATA[A] INDICATING THE RELATIVE CAFFEINE CONTENT OF THE FOLLOWING BEVERAGES:

	MEDIAN MG PER 225 ML SERVING	
1. COFFEE		
A. INSTANT	66	
B. PERCOLATED	74	
C. DRIP OR FILTER	112	
MEAN	84	ROUGHLY 3:1:1 RATIO
2. TEA	27	
3. COLA (10 OZ.)	31	

EACH MEASURE WAS CHECKED FOR NORMALITY OF DISTRIBUTION. SINCE BOTH CAFFEINE MEASURES WERE POSITIVELY SKEWED (SKEW > 2.0), THEY WERE NORMALIZED BY LOG TRANSFORMATIONS.

[A] GILBERT, MARSHMAN, SCHWIEDER, & BERG (1976); BARR, STREISSGUTH, MARTIN, & HORST (1981).

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TABLE 2

INFANT OUTCOME MEASURES

A. ANTHROPOMETRIC MEASURES
   1. BIRTHWEIGHT (GM)
   2. CROWN-HEEL LENGTH (CM)
   3. HEAD CIRCUMFERENCE (CM)

B. GESTATIONAL AGE BASED ON
   1. OBSTETRICIAN'S ESTIMATED DATE OF CONFINEMENT
   2. BALLARD SCALE OF FETAL MATURATION (BALLARD, NOVAK, & DRIVER, 1979) (DAY 2)

C. NEONATAL BEHAVIORAL ASSESSMENT SCALE (NBAS; BRAZELTON, 1973) (DAY 3)
   1. CLUSTERS (JACOBSON, FEIN, JACOBSON, & SCHWARTZ, 1984).
      A. RESPONSE DECREMENT
      B. ORIENTATION
      C. TONICITY
      D. REGULATION OF STATE
      E. RANGE OF STATE
      F. AUTONOMIC MATURITY
      G. REFLEXES
   2. GENERAL IRRITABILITY RATING SCALE (NBAS-K, HOROWITZ, SULLIVAN, & LINN, 1978)

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TABLE 3

CORRELATIONS OF CAFFEINE USE WITH 30 POTENTIAL CONFOUNDING VARIABLES (N = 313)

POTENTIAL CONFOUNDS	CAFFEINE	
	PRIOR	DURING
BACKGROUND		
SOCIOECONOMIC STATUS (SES)[A]	-.10+	-.18**
MATERNAL AGE	.13*	.08
MATERNAL EDUCATION (YEARS)	-.01	-.15*
PARITY	.05	.21***
GRAVIDITY	.02	.09
MATERNAL PREGRAVID WEIGHT	-.04	-.00
MATERNAL HEIGHT	.00	-.06
MATERNAL BODY MASS[B]	-.04	.02
SEX OF INFANT	.00	-.00
PREGNANCY AND DELIVERY		
STRESS[C]	.03	.06
PRENATAL CARE (MONTHS)	-.09	-.02
WEIGHT GAIN (DURING PREGNANCY)	-.09	-.08
LENGTH OF LABOR (HOURS)	.04	-.05
TYPE OF DELIVERY (SPONTANEOUS/OTHER)	-.06	-.06
OBSTETRICAL COMPLICATIONS SCORE[D]	.00	-.08
OBSTETRICAL MEDICATION		
VISTARIL INTRAMUSCULAR (MG)	.02	-.07
CARBOCAINE PUDENDAL	.06	.09
XYLOCAINE PUDENDAL	.03	.00
XYLOCAINE LOCAL	.02	.04
OXYTOCIN (HOURS OF ADMINISTRATION)	.01	.01
SMOKING AND ALCOHOL USE		
SMOKING PRIOR TO PREGNANCY[E]	.19**	.26***
SMOKING DURING PREGNANCY[E]	.14*	.33***
ALCOHOL PRIOR TO PREGNANCY[F]	.07	.08
ALCOHOL DURING PREGNANCY[F]	.09	.22***

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CORRELATIONS OF CAFFEINE USE WITH 30 POTENTIAL CONFOUNDING VARIABLES (N = 313)

(CONTINUED)

POTENTIAL CONFOUNDS	CAFFEINE	
	PRIOR	DURING
OTHER DRUGS		
ASPIRIN	.10+	.17**
ACETOMINOPHEN	.16**	.16**
COLD REMEDIES	.03	.04
ANTACIDS	.16**	.09
ANTIBIOTICS	-.03	-.04
PCB EXPOSURE[G]	.12*	.10+

NOTE: ALL CONTROL VARIABLES WHICH CORRELATED WITH CAFFEINE USE AT AN ALPHA LEVEL LESS THAN OR EQUAL TO .10 WERE CONSIDERED POTENTIAL CONFOUNDS AND INCLUDED IN SUBSEQUENT REGRESSION ANALYSES.

[A]HOLLINGSHEAD AND REDLICH (1958).

[B]BASED ON EQUATION $\frac{\text{WEIGHT (KG)}}{\text{HEIGHT (M)}^{1.5}}$

[C]BASED ON MATERNAL REPORT OF FAMILY ILLNESS OR DEATH, UNEMPLOYMENT, MARITAL PROBLEMS, OR OTHER STRESS DURING PREGNANCY.

[D]BASED ON THE OBSTETRICAL COMPLICATIONS SCALE (LITTMAN & PARMELEE, 1978). HIGHER SCORESS REFLECT FEWER COMPLICATIONS.

[E]BASED ON PACKS OF CIGARETTES PER DAY.

[F]BASED ON DAILY INGESTION OF ABSOLUTE ALCOHOL (AA), ESTIMATED FROM REPORTED RATE OF BEER, WINE, AND HARD LIQUOR (KUZMA & KISSINGER, 1981).

[G]BASED ON MATERNAL CONSUMPTION OF PCB CONTAMINATED FISH (JACOBSON, JACOBSON, SCHWARTZ, & FEIN, 1983).

+$p < .10$
*$p < .05$
**$p < .01$
***$p < .001$

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TABLE 4

INFANT OUTCOMES ASSOCIATED WITH CAFFEINE USE BEFORE AND DURING PREGNANCY

OUTCOME	CAFFEINE					
	PRIOR			DURING		
	BETA	D.F.	F	BETA	D.F.	F
BIRTHWEIGHT	-.18	1,285	6.65**	.09	1,286	1.28
NEONATAL BEHAVIORS						
ORIENTATION	-.17	1,219	4.24*	.11	1,221	1.37
RANGE OF STATE	.15	1,266	4.19*	.07	1,268	.07
GENERAL IRRITABILITY	.16	1,268	4.49*	.07	1,270	.66
NEONATAL BEHAVIORS (CONTROLLING FOR BIRTHWEIGHT)[A]						
ORIENTATION	-.15	1,213	3.53+	--	--	--
RANGE OF STATE	.11	1,260	3.89*	--	--	--
GENERAL IRRITABILITY	.16	1,262	4.49*	--	--	--

NOTE: F-RATIOS TEST THE STATISTICAL SIGNIFICANCE OF THE UNIQUE VARIANCE ASSOCIATED WITH CAFFEINE CONSUMPTION, AFTER CONTROLLING FOR THE EFFECTS OF THE ASSOCIATED POTENTIAL CONFOUNDING VARIABLES. BECAUSE OF POSSIBLE MULTICOLLINEARITY INVOLVING SES AND MATERNAL EDUCATION, ONLY SES WAS USED AS A POTENTIAL CONFOUND OF CAFFEINE USE DURING PREGNANCY. CAFFEINE PRIOR AND DURING WERE INCLUDED IN ALL REGRESSIONS, IN ORDER TO ASSESS THE UNIQUE VARIANCE ATTRIBUTABLE TO EACH.

[A]TESTS THE HYPOTHESIS THAT THE BEHAVIORAL OUTCOMES WERE MEDIATED BY THE EFFECT OF BIRTHWEIGHT. SINCE THE F-RATIO REMAINS SIGNIFICANT FOR RANGE OF STATE AND IRRITABILITY THE CAFFEINE EFFECT ON THESE BEHAVIORS APPEARS DIRECT AND NOT MEDIATED BY SIZE.

+$p < .10$

*$p < .05$

**$p < .01$

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TABLE 5

RELIABILITY COEFFICIENTS FOR SMOKING, ALCOHOLIC, AND CAFFEINATED BEVERAGES FOR CONSUMERS ONLY (N = 57)

SUBSTANCE	N	PRIOR	DURING
CAFFEINE	57	.78**	.33*
COFFEE	39	.78**	.64**
TEA	39	.61**	.81**
CAFFEINATED SOFT DRINKS	47	.66**	-.01

NOTE: COEFFICIENTS ARE CALCULATED FOR ALL MOTHERS WHO REPORTED DRINKING A PARTICULAR BEVERAGE PRIOR TO PREGNANCY.

* $p < .05$
** $p < .001$

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TABLE 6

VALIDITY COEFFICIENTS FOR SMOKING, ALCOHOLIC, AND CAFFEINATED BEVERAGES FOR CONSUMERS ONLY (N = 29)

SUBSTANCE	N	
CAFFEINE	29	.82*
COFFEE	18	.81*
TEA	17	.65*
CAFFEINATED SOFT DRINK	24	.21

NOTE: VALIDITY COEFFICIENTS ARE CALCULATED FOR THE 29 MOTHERS WHO RETURNED COMPLETED DAILY RECORDS.

*$P < .001$

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FIGURE 1

FREQUENCY DISTRIBUTION FOR CAFFEINE USE BEFORE AND DURING PREGNANCY (N=309)

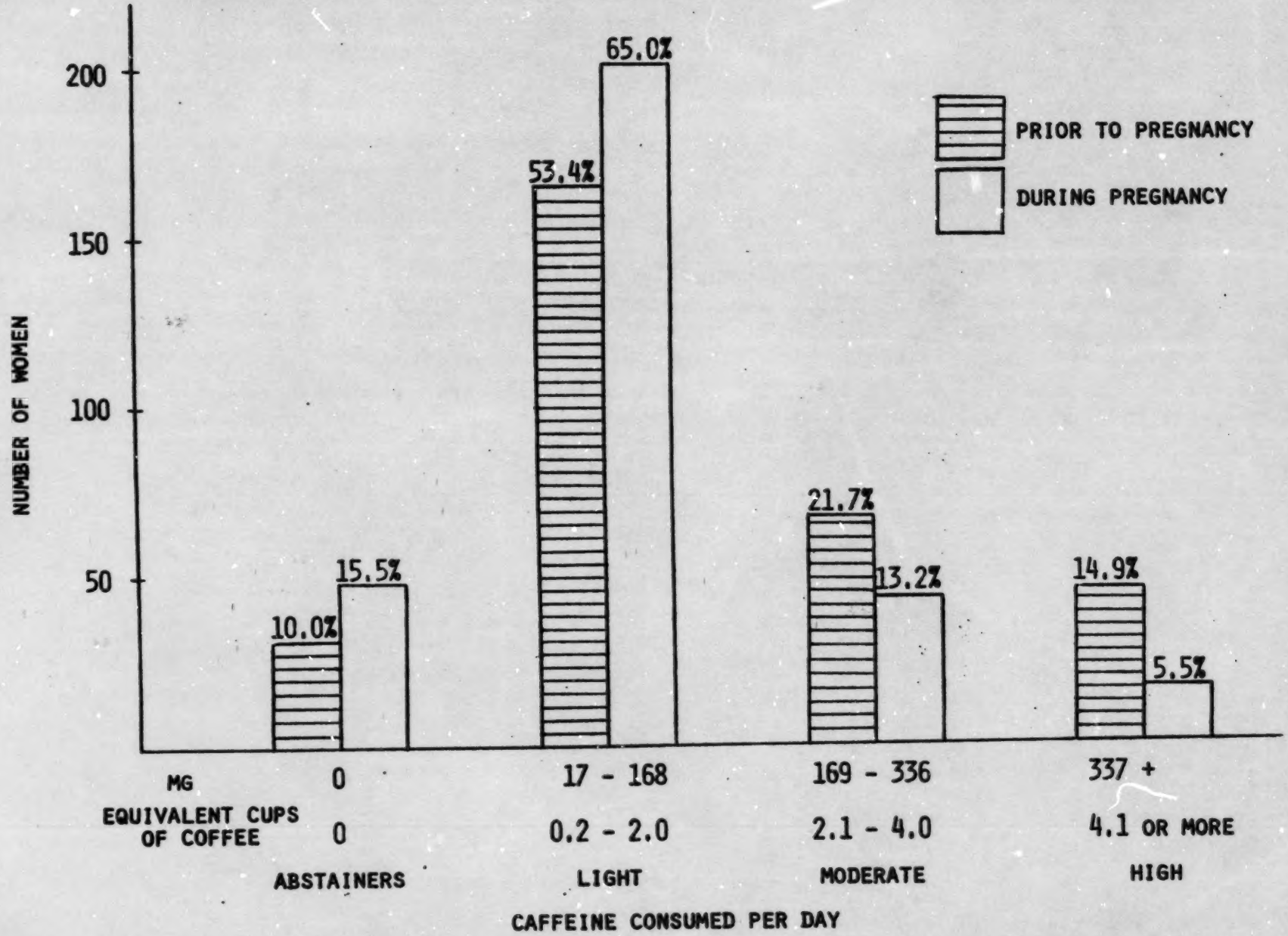

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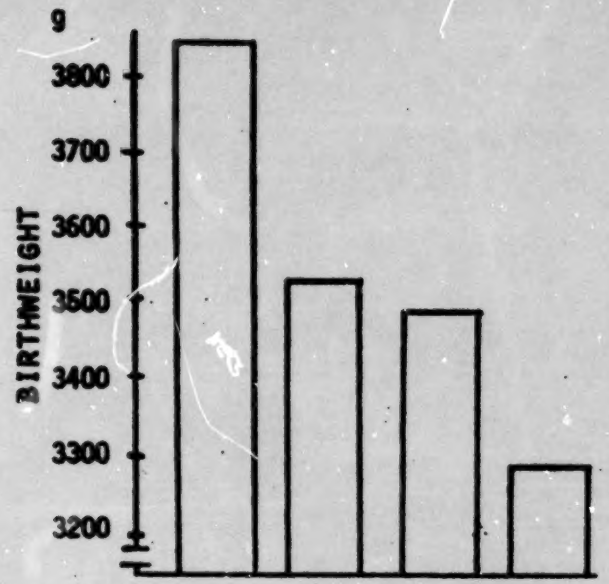
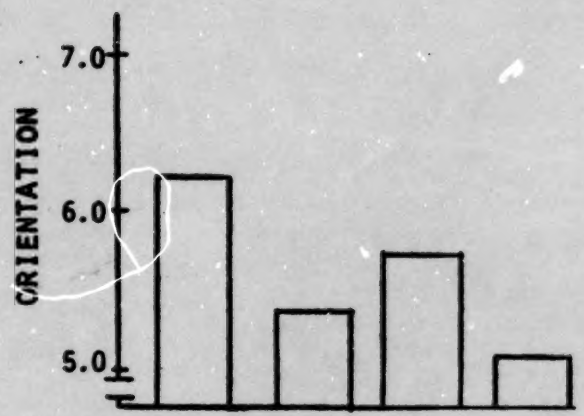
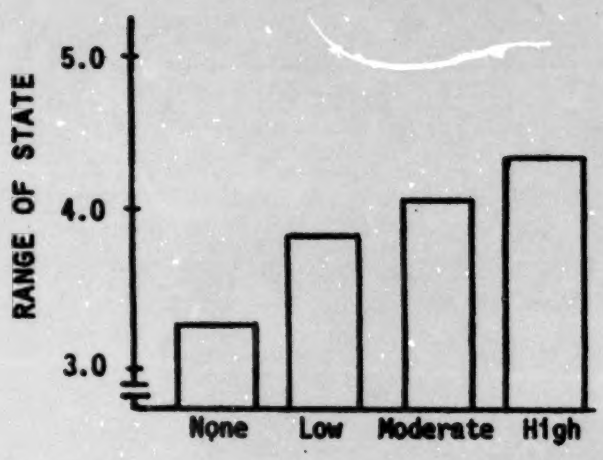
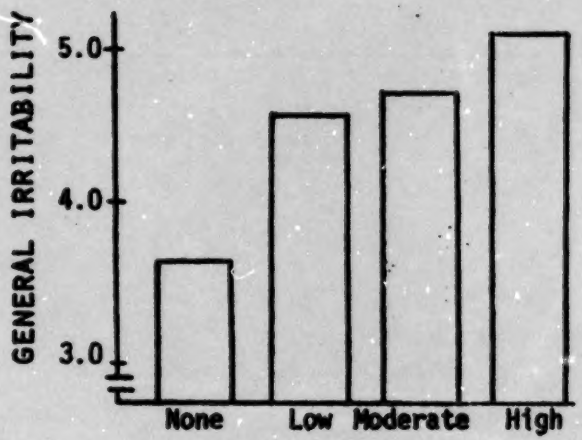
FIGURE 2







CAFFEINE USE PRIOR TO PREGNANCY



CAFFEINE USE PRIOR TO PREGNANCY

DOSE RESPONSE RELATIONSHIP FOR THE EFFECTS OF CAFFEINE PRIOR TO PREGNANCY ON BIRTHWEIGHT, ORIENTATION, RANGE OF STATE, AND GENERAL IRRITABILITY, AFTER ADJUSTING FOR THE ASSOCIATED POTENTIAL CONFOUNDS, INCLUDING CAFFEINE USE DURING PREGNANCY.

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